Structural determinants of lumen narrowing after angioplasty in atherosclerotic nonhuman primates

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Purpose: The relationship between lumen narrowing, intimal hyperplasia, and wall remodeling after angioplasty was explored in a nonhuman primate model of atherosclerosis.

Methods: Cynomolgus monkeys (n = 37) used in long-term atherosclerosis studies underwent left iliac artery balloon injury. The uninjured right iliac artery served as a reference segment for intraanimal comparisons. One month later iliac arteries were fixed by perfusion (100 mm Hg) and removed for cross-sectional analysis to determine mean values for lumen area (LA), intimal area (IA), internal elastic lamina area (IELA), plaque burden (IA/IELA), and depth of wall injury. Values for each balloon-injured iliac artery were normalized to the contralateral uninjured iliac artery (percent of control), and linear regression analysis was performed comparing LA with IA, with IELA, and with depth of injury. Comparisons were also made between those arteries that remained dilated 1 month after balloon injury (LA ≥ 140%; n = 13) and those that renarrowed (LA ≤ 100%; n = 14).

Results: For all 37 animals, LA 1 month after balloon injury correlated well with IELA ($r = 0.72$; $p < 0.001$) but not with IA ($r = 0.10$; $p = 0.54$), suggesting that changes in artery size rather than neointimal mass determined lumen caliber. When comparing arteries that remained dilated (n = 13) with those that renarrowed (n = 14), there were no differences in depth of wall injury (injury depth: 0, no injury; 1, intima; 2, IEL; 3, media; 4, EEL; 2.1 ± 0.3 vs 1.6 ± 0.3; $p = 0.12$), neointimal accumulation (IA, 507% ± 118% vs. 421% ± 81% of control; $p = 0.55$), or plaque burden (IA/IELA, 0.39 ± 0.04 vs 0.37 ± 0.06; $p = 0.71$), respectively. However, wall size defined as IELA was significantly smaller in arteries that renarrowed than in those that remained dilated (IELA, 115% ± 14% vs 230% ± 19% of control; $p < 0.001$).

Conclusions: Restenosis after angioplasty has been attributed to intimal hyperplasia, equating loss of lumen caliber with neointimal mass. The data presented herein suggest that lumen narrowing after arterial wall injury may have little to do with intimal mass per se, but rather that a change in wall caliber or wall narrowing is the cause of restenosis. (J Vasc Surg 1997;26:875-83.)

The loss of lumen caliber after angioplasty (restenosis) has commonly been attributed to lumen encroachment by accumulation of intimal mass. This hypothesis has recently been called into question by the observation that lumen narrowing both in atherosclerosis[1-3] and in restenosis after angioplasty[4-8] does not correlate with intimal mass.

In part, questions about intimal hyperplasia and lumen encroachment as the critical step in restenosis arise from drug trials with agents directed at inhibiting smooth muscle cell (SMC) proliferation after angioplasty (i.e., converting enzyme inhibitors, heparins, etc.). Drugs that are effective at preventing intimal hyperplasia in animal models[9,10] have consistently failed to prevent restenosis in clinical trials.[11-13] This failure could be a result of (1) species differences in SMC growth regulation[14]; (2) inadequate experimental modeling of advanced human atherosclerosis and, as a consequence, a poor understanding of the contribution of a preexisting lesion to the injury

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0741-5214/97/$5.00 + 0 **24/6/85090**

response[5]; or (3) the intimal hyperplasia hypothesis equating intimal growth with lumen narrowing may simply be wrong.[15,16]

If intimal hyperplasia is not the mechanism of restenosis, pathologic narrowing of the lumen could depend on a rearrangement of the components of the artery wall rather than loss of lumen caliber as a result of expansion of intimal lesions. This rearrangement has been called "remodeling." Recent studies in a unique nonhuman primate model of atherosclerosis have suggested that lumen narrowing after angioplasty occurs independent of intimal hyperplasia.[5] We herein extend these initial observations by analyzing the structural response of iliac arteries in 37 atherosclerotic monkeys 1 month after balloon injury. Our hypothesis was that lumen renarrowing after balloon injury was caused by a failure of vessel wall remodeling to accommodate intimal hyperplasia and that lumen narrowing would be determined by a decrease in artery wall size rather than intimal mass per se. Cross-sectional analysis of balloon-injured arteries in the present study supports the concept of restenosis as a failure of remodeling.

METHODS

Animal model. Animals in this study comprised a subset of atherosclerotic monkeys from our institution that underwent left iliac artery balloon injury (n = 37). All iliac arteries were retrieved at necropsy 1 month after balloon injury. Twenty-four male and 13 surgically postmenopausal (ovariectomized) female cynomolgus monkeys *(Macaca fascicularis)* were fed an atherogenic diet for 3 to 5 years to establish complex atherosclerotic lesions. The diet contained 0.28 mg cholesterol per calorie and was composed of 17% protein, 38% carbohydrate, and 45% lipid (46% saturated, 43% monounsaturated, and 11% polyunsaturated fatty acids). Balloon injuries were then performed with the monkey under anesthesia with ketamine hydrochloride (10 mg/kg intramuscular injection) and butorphanol (0.05 mg/kg intramuscular injection). The depth of anesthesia was closely monitored, and animals were given more drug as necessary. The left femoral vessels were exposed in the groin, and control of the left common femoral artery was obtained. A 3F balloon catheter (Fogarty Arterial Embolectomy Catheter, Baxter Healthcare Corp., Irvine, Calif.) was passed through a transverse arteriotomy into the distal abdominal aorta, inflated, and retrieved under moderate tension three times across the left common iliac artery segment. The femoral arteriotomy was then repaired, the wound was closed in layers, and antibiotic was administered (cefazolin sodium, 25 mg/kg intramuscular injection). Animals recovered in individual cages and then returned to group housing.

The monkeys were killed 1 month after balloon injury. The monkeys were again sedated with ketamine and butorphanol, anticoagulated with heparin (300 U/kg intravenous injection), and then deeply anesthetized with sodium pentobarbital (100 mg/kg intravenous injection). The distal abdominal aorta was cannulated, and the iliac arteries were perfused in situ at physiologic pressure (100 mm Hg) with lactated Ringer's solution until clear of blood and then were perfused with 10% neutral buffered formalin for 1 hour. The distal aorta and iliac arteries were removed en bloc and placed into fresh formalin for 36 hours before paraffin embedding.

All animal care and procedures were performed at the Comparative Medicine Clinical Research Center of the Bowman Gray School of Medicine in accordance with state and federal laws. Animal protocols were approved by the Bowman Gray Animal Care and Use Committee and conformed to guidelines set forth in the "Principles of Laboratory Animal Care" (formulated by the National Society for Medical Research) and the *Guide for the Care and Use of Laboratory Animals* (National Institutes of Health publication No. 86-23, revised 1985).

Histologic and morphometric analysis. Fixed common iliac arteries were cut into five adjacent rings of equal length for paraffin embedding. Sections 5 μm thick were cut from each ring, mounted onto glass slides, and stained with Verhoeff–van Gieson stain for morphometric analysis. A videomicroscopic image of each slide was captured using a Power Macintosh and frame grabber and was digitized. The luminal area (LA) and internal elastic lamina area (IELA) were measured for each ring (Fig. 1) using the public domain NIH Image program (developed at the National Institutes of Health, available via the Internet, FTP from zippy.nimh.nih.gov or on floppy disk from the National Technical Information Service, Springfield, Va., part number PB95-500195GEI). The intimal area (IA) and plaque burden (IA/IELA) were calculated for each section from these measurements. An injury grade was assigned to each section on the basis of the depth of vessel wall disruption using a modification of the schema reported by Schwartz et al.[17] (Table I). Mean values for each iliac artery (balloon-injured and uninjured) were determined by averaging values from each of the five adjacent rings.

To control for the differences in animal size, and therefore baseline artery size, values from each bal-

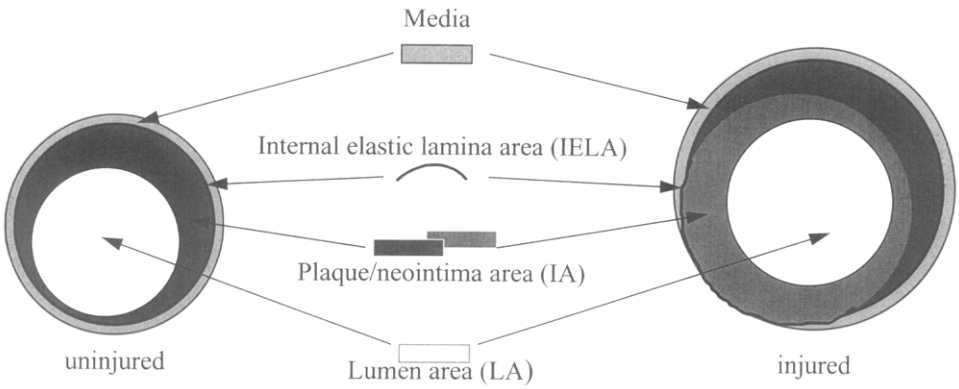

Fig. 1. Diagram of morphometry measurements made in each iliac artery ring. In the text, *IELA* refers to the area bounded by the internal elastic lamina (plaque/neointima and lumen). *IA* refers to plaque in uninjured arteries and plaque plus neointima in injured arteries. Medial area was not different in injured and uninjured arteries and was not included in subsequent analyses.

loon-injured artery were normalized to those of the contralateral uninjured iliac artery within individual animals and expressed as a fraction of the uninjured iliac IA, LA, or IELA. Previous studies by our group have shown that artery and plaque size in right and left common iliac arteries are similar within an individual animal (IA, $r = 0.98$ and $r = 0.97$; LA, $r = 0.90$ and $r = 0.87$, for the male group [n = 109] and the female group [n = 203], respectively).[5] In this model, true stenosis (angiographically or hemodynamically significant luminal narrowing) is found sporadically as a result of remodeling and arterial wall accommodation for enlarging plaques.[2] For the purposes of this study, loss of luminal gain or "restenosis" was defined as a final lumen area less than or equal to that of the contralateral uninjured iliac artery (LA 100% of control or less). To provide maximal contrast among groups for subset analysis, an equal number of animals were selected that had maintained the greatest amount of lumen dilation, for comparison (LA 140% of control or greater; n = 13).

Statistical analysis. The values that were measured and calculated for each of the five sections were averaged to derive the mean for each artery studied. Mean values were then entered into a spreadsheet for further analysis (Excel, v. 7.0a for Windows 95, Microsoft Corp., Seattle, Wash.). For the entire cohort (n = 37), relationships between normalized LA and normalized IA and IELA, and injury grade were investigated using linear regression analysis with significance determined by analysis of variance. A subset analysis was then performed, comparing a group that demonstrated the most lumen narrowing ("restenosis," n = 14) and the group that maintained the greatest luminal dilation ("no restenosis," n = 13) using the unpaired, two-tailed Student's t test. All statistics were performed in Microsoft Excel. A p value less than or equal to 0.05 was considered to indicate a statistically significant difference. All values are reported as the mean of means ± SEM unless otherwise specified.

Table I. Grading of arterial injury depth

Injury grade	*Histologic correlate*
0	No injury
1	Plaque rupture
2	Internal elastic lamina torn
3	Medial tear
4	External elastic lamina torn

RESULTS

Plasma lipids. Study animals were involved in long-term atherosclerosis research at the Comparative Medicine Clinical Research Center of the Bowman Gray School of Medicine. The cynomolgus monkey model of atherosclerosis has previously been shown to closely mimic human lesion progression.[2] Study animals had a mean total plasma cholesterol level of 417 mg/dl (range, 126 to 706 mg/dl) and mean high-density lipoprotein level of 48 mg/dl (range, 31 to 94 mg/dl). The mean lipoprotein (a) level was 30 mg/dl (range, 0.5 to 98.9 mg/dl). Plasma lipid parameters were not significantly different between the "restenosis" and "no restenosis" groups ($p = 0.51$, $p = 0.08$, and $p = 0.77$, respectively).

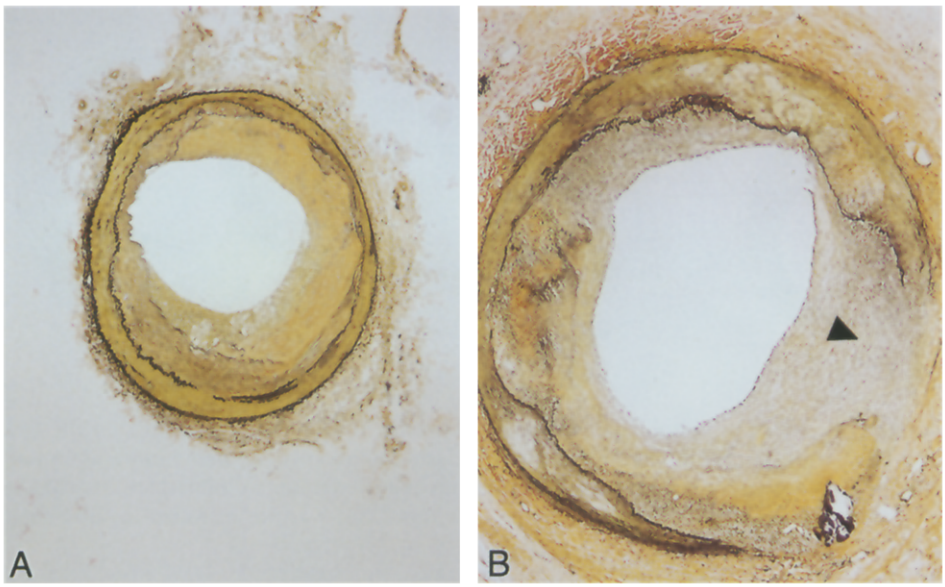

Fig. 2. Composite photomicrograph demonstrates uninjured iliac artery **(A)** and contralateral injured iliac artery **(B)** in an atherosclerotic cynomolgus monkey 1 month after balloon angioplasty. A complicated preexisting atherosclerotic plaque was fractured *(arrowhead)* and is seen underlying a significant accumulation of neointima. Sections were stained with Verhoeff–van Gieson stain and photographed at an original magnification of 40×.

Iliac artery morphometry. In this model, balloon injury results in distention of the vessel, which is accompanied by a variable degree of disruption of the layers of the artery wall (Fig. 2). As we have previously shown, lumen dilation is significant at 4 days after balloon injury (mean LA, 232% of uninjured).[5] However, over the ensuing month, the initial gain in lumen caliber is variably lost in some animals, which results in a spectrum of normalized LAs (Fig. 3). For the entire cohort of animals in this study, balloon injury resulted in moderate persistent dilatation at 1 month (IELA, 174% ± 12% of control; LA, 126% ± 9% of control) despite significant neointimal accumulation (IA, 418% ± 55% of control). Similar to data reported in human clinical angioplasty series, approximately one third of the animals demonstrated a significant loss of the acute gain in lumen caliber, whereas the remainder maintained some degree of the luminal dilation after balloon injury. Although gender affects baseline artery size, when normalized to the uninjured iliac within each animal, there were no gender differences in the iliac response to balloon injury. LA, IA, IELA, and injury extent were similar in the male and female groups 1 month after iliac balloon injury ($p > 0.16$ for all endpoints).

Fig. 4 illustrates the relationships between the normalized LA (dependent variable) and normalized IA and IELA (independent variables) in all 37 balloon-injured iliac arteries. Linear regression analysis demonstrated a poor correlation between LA and IA (LA vs IA; $r = 0.10$, $p = 0.54$) and between LA and depth of injury (LA vs injury grade; $r = 0.25$, $p = 0.14$). In contrast, there was a highly significant correlation between LA and the artery wall size (LA vs IELA; $r = 0.72$, $p << 0.001$). In contrast to the results of reports in other models,[17] injury extent did not correlate with the change in IA (IA vs injury grade; $r = 0.21$, $p = 0.21$). These relationships were the same for the male group and the female group when analyzed separately.

Of the 37 animals that were studied, 14 (37.8%) had a final LA less than or equal to 100% of the uninjured reference (restenosis), whereas an equal number of animals (n = 13; 35.1%) maintained an LA greater than or equal to 140% of the uninjured reference value (no restenosis; Table II). There was a trend towards larger arteries at baseline in the restenosis group, although this trend did not reach statistical significance (uninjured IELA, 3.85 ± 0.42 mm^2 vs 2.85 ± 0.29 mm^2; restenosis vs no restenosis, $p = 0.06$). There was no significant difference in the depth of wall disruption in the balloon-injured iliac arteries (injury grade, 1.6 ± 0.3 vs 2.1 ± 0.3; restenosis vs no restenosis, $p = 0.12$). In both of the groups, balloon injury induced significant intimal hyperplasia. However, there was no difference in in-

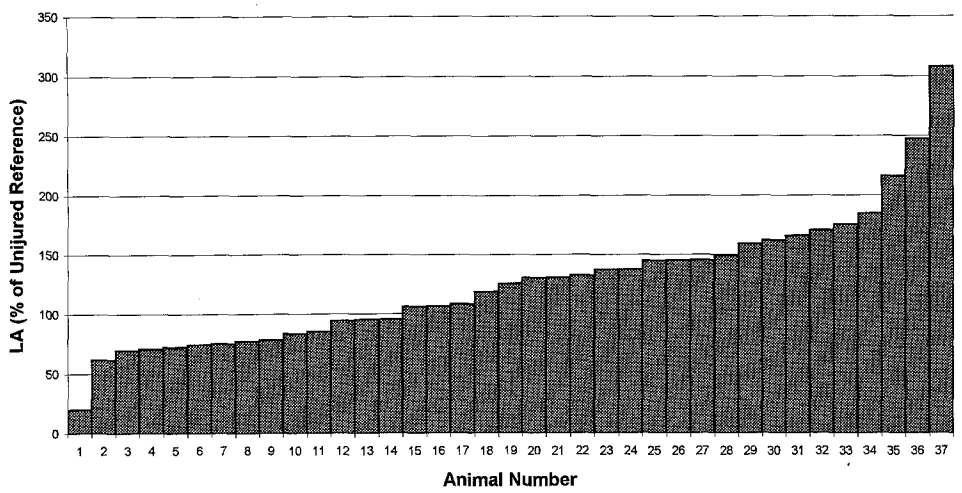

Fig. 3. Bar chart shows range of normalized LAs in 37 animals 1 month after iliac artery balloon injury. One third demonstrate significant loss of the initial gain in LA relative to the uninjured reference (LA ≤ 100% of uninjured control), whereas the remainder demonstrate some persistent lumen dilation.

timal hyperplasia in response to the balloon injury nor in the plaque burden between the two groups (IA, 421% ± 81% vs 507% ± 118% of uninjured control, $p = 0.55$; plaque burden [IA/IELA], 0.37 ± 0.05 vs 0.39 ± 0.04, $p = 0.71$, restenosis vs no restenosis, respectively). There was, however, a significant difference between groups in the change in artery size after balloon injury. Animals that demonstrated restenosis maintained significantly less of the initial increase in artery wall size that was caused by balloon injury (IELA, 115% ± 14% vs 230% ± 19% of uninjured control; $p << 0.001$), which suggests that wall narrowing contributed to lumen narrowing (Fig. 5).

DISCUSSION

Restenosis, or the failure to maintain adequate lumen caliber after angioplasty and other forms of vascular reconstruction, remains an important obstacle in the treatment of patients with atherosclerotic vascular disease and affects a large proportion of vascular interventions.[18-20] Of necessity, angioplasty, endarterectomy, and anastomoses cause injury to the vessel wall, and the physiologic response to these injuries sets the stage for either success or failure in maintaining lumen caliber. In many nonatherosclerotic animal studies, neointimal hyperplasia was viewed as the major factor that determined lumen caliber after angioplasty.[21] More recent analyses in similar models[6-8,22] and clinical data emerging from the use of intravascular ultrasound[4] demonstrate the importance of arterial wall structure in the maintenance of adequate lumen caliber. Despite the increasing interest in these phenomena, the relative roles of intimal hyperplasia and changes in arterial wall structure in restenosis remain unclear.

In this report, we have expanded on our initial observations on the structural changes that occur in arteries after balloon injury in a nonhuman primate model of atherosclerosis. Our findings suggest that intimal hyperplasia is a normal and consistent component of the injury response in atherosclerotic arteries; however, neointimal mass plays a limited role in lumen narrowing after balloon injury.[5] In this model, there is a strong correlation between final artery size (IELA) and the gain or loss of lumen caliber after balloon injury; however, there is no correlation between the size of the neointima and final LA. One month after balloon injury, the degree of intimal accumulation and plaque burden were no different between those animals that demonstrated the greatest loss of lumen caliber and those that maintained the most lumen dilation. On the other hand, artery size was significantly smaller in arteries that lost lumen caliber. Thus in this model restructuring of the arterial wall, not accumulation of neointimal mass, was the predominant mechanism that determined success or failure in maintaining lumen caliber after balloon injury.

The concept of vascular remodeling comes from physiologists and developmentalists, who have used the term to describe adaptive changes in artery wall structure in response to altered hemodynamic forces. The lumen caliber and wall thickness increase to

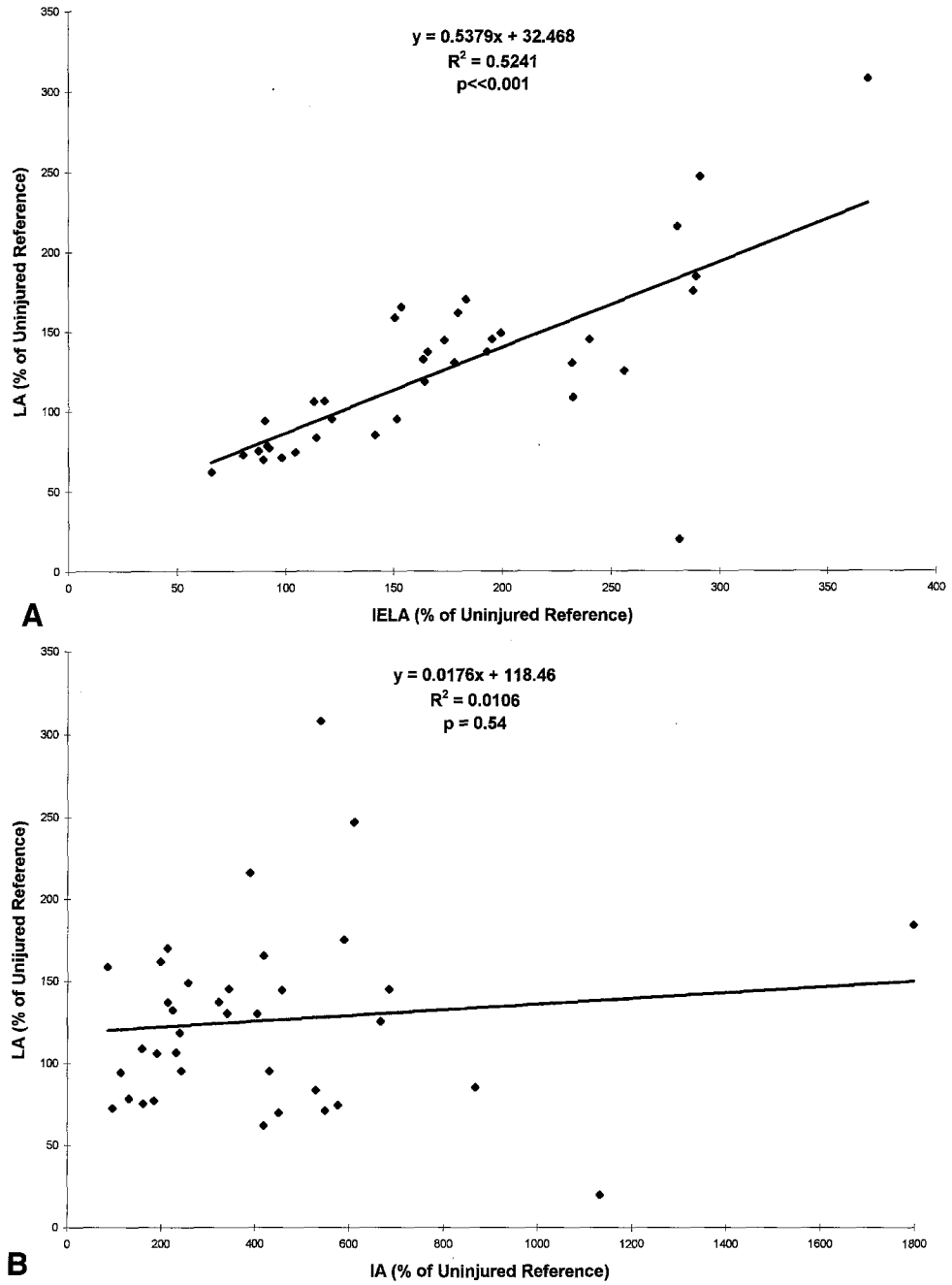

Fig. 4. Scatter plots with regression lines for normalized LA compared with normalized IELA **(A)** and compared with normalized IA **(B)** of injured iliac arteries from 37 atherosclerotic cynomolgus monkeys. Lumen caliber and artery size are closely related ($r = 0.72$), whereas a poor correlation exists between lumen caliber and intimal mass ($r = 0.10$).

maintain shear stress and wall tension within a physiologic range. These responses are central to the homeostasis of vascular circuitry. As arteries age and develop atherosclerosis, similar remodeling occurs.[1,2] The artery wall enlarges to accommodate intimal thickening and thereby preserve lumen caliber and end-organ blood flow. In this sense, remodeling is a normal physiologic process by which arteries maintain optimal geometry, and stenosis develops only when remodeling fails. A similar mechanism may be important in restenosis, where lumen narrowing may represent a failure of wall remodeling to accommo-

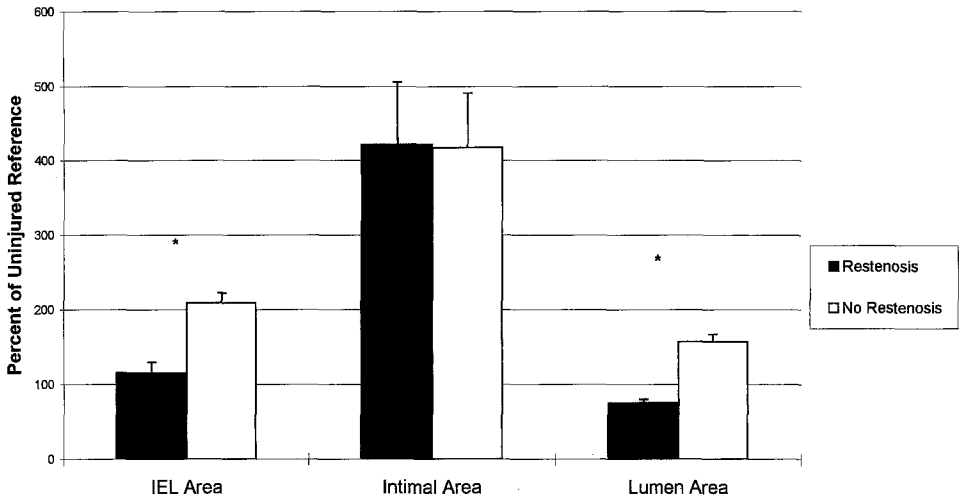

Fig. 5. Bar chart compares normalized LA, IA, and IELA in arteries demonstrating restenosis (LA ≤ 100% of control) and those with no restenosis (LA ≥ 140% of control) after angioplasty. Both groups had a similar marked increase in intimal mass; however, final LA was mirrored by changes in artery wall size. $*p < 0.001$, restenosis vs no restenosis.

Table II. Iliac artery morphometry 1 month after balloon injury

	Restenosis (n = 14)	*No restenosis (n = 13)*	*p*
Artery size (IELA)	3.99 ± 0.28 mm^2	6.64 ± 0.93 mm^2	0.02
(normalized to uninjured reference [%])	(115% ± 14%)	(230% ± 19%)	(≪0.001)
Intimal area (IA)	1.44 ± 0.26 mm^2	2.56 ± 0.39 mm^2	0.03
(normalized to uninjured reference [%])	(421% ± 81%)	(507% ± 118%)	(0.55)
Plaque burden (IA/IELA)	0.37 ± 0.05	0.39 ± 0.04	0.71
(normalized to uninjured reference [%])	(335% ± 49%)	(205% ± 41%)	(0.06)
Lumen area (LA)	2.53 ± 0.31 mm^2	3.88 ± 0.6 mm^2	0.07
(normalized to uninjured reference [%])	(75.1% ± 5.9%)	(182% ± 13.4%)	(≪0.001)
Injury grade	1.6 ± 0.3	2.1 ± 0.3	0.12

date neointimal growth or narrowing of the wall from tissue contraction analogous to wound healing.

Our data are consistent with the concept of compensatory remodeling (accommodation), as has been suggested in primary atherosclerosis. Glagov and colleagues,[1] and more recently Clarkson et al.[2] and others[3] have shown convincingly that human coronary and peripheral arteries enlarge to accommodate intimal growth from atherosclerosis. A similar mechanism appears to occur in response to angioplasty, whereby the ability to accommodate neointimal growth caused by wall injury is the primary determinant of final LA. One could then view both stenosis from primary atherosclerosis and restenosis after vascular intervention as failures of the normal compensatory response of remodeling.

The etiologic mechanism of this failure to remodel remains to be elucidated. Similarities between the remodeling response to angioplasty and generalized wound healing elsewhere in the body may provide a useful paradigm for analysis. It must be emphasized that the arterial wounds that are relevant to stenosis and restenosis occur in a pathologic tissue, the atherosclerotic intima, that has unique properties that may alter the way a vessel responds to injury. In the present monkey model, as with angioplasty in human beings, balloon injury increases lumen caliber by fracturing the preexisting plaques and by stretching or tearing the overlying media and adventitia.[5] Subsequent formation of mural thrombus provides a provisional matrix into which SMCs, inflammatory cells, and possibly myofibroblasts migrate to form a neointima. By 1 week, SMCs within this neointima express matrix molecules and a variety of integrins ($\alpha_v\beta_3$ and $\alpha_2\beta_1$) that may contribute significantly to the contraction of extracellular matrix components

within the artery wall (Geary RL, unpublished observations, 1997). Contraction of these wounds, as in cutaneous wounds, may then impair or prevent remodeling and accommodation and predispose the injury site to restenosis. Use of blocking antibodies to specific integrins that are important in wound contraction has shown promising results in cell culture[23] and in a rabbit model of carotid balloon injury.[24] Recently, human angioplasty trials have documented a significant reduction in late deaths, myocardial infarction, and the need for target vessel revascularization in patients who were treated with a β_3-integrin antagonist.[25,26] Whether these improvements are a result of an antiplatelet effect or to decreased restenosis is unclear, but we and others have speculated that inhibition of integrin-mediated tissue contraction could have played a role. Further studies are needed to confirm this speculation and that the behavior of the artery wall may influence lumen caliber independent of the amount of neointimal accumulation.

Although the present study supports the findings that have been reported previously by our group and others, potential limitations must be considered. The regression analysis that we used cannot prove cause and effect, but rather demonstrates that there is a significant association between artery wall size, structure, and final LA after balloon injury. However, when taken in the context of our previous time-course study in this model, in which the artery wall appeared to increase on average during the period of most rapid intimal growth, both studies are consistent with the remodeling hypothesis. Elucidation of a cause and effect relationship will require serial analysis of individual vessels using repeated arteriography, Duplex imaging, or intravascular ultrasound, and these studies are currently underway.

Although nonhuman primates represent a well-characterized animal model of human atherosclerosis,[2,27,28] the model itself has several shortcomings. True stenosis at the site of subsequent iliac balloon injury is only sporadically present. Thus the lumen narrowing demonstrated at 1 month is often not truly "restenosis," but rather loss of the initial gain in lumen caliber after balloon injury in an atherosclerotic artery. In addition, the injury produced by the embolectomy catheter may differ from that induced by a standard Gruentzig-type angioplasty catheter. The Fogarty catheter injury is likely to denude more endothelium and produce longitudinal shear. However, we have previously documented that the preexisting plaque is not removed by this procedure,[5] and a striking similarity exists in the appearance of these injured arteries and those from standard angioplasties as documented by histologic evaluation and intravascular ultrasound.[29,30] Moreover, we have found that the embolectomy catheter method produces a more consistent injury in this monkey model. The perfect model remains the human patient. However, until noninvasive techniques such as magnetic resonance angiography, Duplex ultrasonography, or intravascular ultrasound achieve suitable resolution with documented correlation with lesion histologic patterns, the use of relevant nonhuman primate models may provide the closest insight.

CONCLUSION

In this well-characterized cynomolgus monkey model of atherosclerosis, we have demonstrated that the lumen caliber 1 month after balloon injury is significantly correlated with artery wall size but not with neointimal mass. Although intimal hyperplasia is a consistent response to balloon injury, it appears that its influence on structural changes of the underlying arterial wall may account for the eventual failure of the normal remodeling process and hence restenosis. Further studies in this model are underway to investigate the failure of remodeling within the paradigm of wound healing and artery wall contracture.

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Submitted Jan. 29, 1997; accepted July 29, 1997.